Iodine-123 Metaiodobenzylguanidine Scintigraphic Assessment of the Transplanted Human Heart: Evidence for Late Reinnervation

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Objectives. This study attempted to determine whether cardiac sympathetic reinnervation occurs late after orthotopic heart transplantation.

Background. Metaiodobenzylguanidine (MIBG) is taken up by myocardial sympathetic nerves. Iodine-123 (I-123) MIBG cardiac uptake reflects intact myocardial sympathetic innervation of the heart. Cardiac transplant recipients do not demonstrate I-123 MIBG cardiac uptake when studied <6 months from transplantation. However, physiologic and biochemical studies suggest that sympathetic reinnervation of the heart can occur >1 year after transplantation.

Methods. We performed serial cardiac I-123 MIBG imaging in 23 cardiac transplant recipients early (≤1 year) and late (>1 year) after operation. In 16 subjects transmyocardial norepinephrine release was measured late after transplantation.

Results. No subject had visible I-123 MIBG uptake on imaging <1 year after transplantation. However, 11 (48%) of 23 subjects developed visible cardiac I-123 MIBG uptake 1 to 2 years after transplantation. Only 3 (25%) of 12 subjects with a pretransplantation diagnosis of idiopathic cardiomyopathy demonstrated I-123 MIBG uptake compared with 8 (73%) of 11 with a pretransplantation diagnosis of ischemic or rheumatic heart disease (p = 0.04). All 10 subjects with a net myocardial release of norepinephrine had cardiac I-123 MIBG uptake; all 6 subjects without a net release of norepinephrine had no cardiac I-123 MIBG uptake.

Conclusions. Sympathetic reinnervation of the transplanted human heart can occur >1 year after operation, as assessed by I-123 MIBG imaging and the transmyocardial release of norepinephrine. Reinnervation is less likely to occur in patients with a pretransplantation diagnosis of idiopathic cardiomyopathy than in those with other etiologies of congestive heart failure.

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Orthotopic cardiac transplantation is now the treatment of choice for suitable patients with end-stage congestive heart failure due to ischemic, idiopathic or other causes. Most transplant recipients have a marked improvement in the quality of life and enjoy 1- and 5-year survival rates of 80% to 90% and 70% to 80%, respectively (1–3). One of the major impediments to further improvement in graft and patient survival is graft coronary vasculopathy (4–8). A particular problem with graft coronary vasculopathy is the lack of signs and symptoms of myocardial ischemia in transplant recipients.

The typical orthotopic cardiac transplantation involves excision of the entire recipient heart except for the posterior atrial walls, to which the donor heart is grafted. The donor sinoatrial node provides the necessary pacemaker activity in the transplanted heart. However, there is severance of autonomic nerves to the grafted heart (1,9). For this reason, silent myocardial ischemia can develop in the setting of graft coronary vasculopathy. To identify the development of graft vasculopathy, most cardiac transplant programs perform annual coronary angiography.

A recent report of chest pain in cardiac transplant recipients suggests that reinnervation of the grafted heart might be possible (10). In addition, an imaging study demonstrated uptake of norepinephrine analogues labeled with positron radionuclides in transplant recipients late after operation (11). We explored the phenomenon of cardiac reinnervation using radioiodinated metaiodobenzylguanidine (MIBG) imaging, which is an analog of the adrenergic false neurotransmitter guanethidine and is taken up by myocardial sympathetic nerves in a manner similar to norepinephrine (12–14). This uptake reflects cardiac adrenergic neuron integrity and function (13,15). We recently found (16) no evidence of cardiac iodine-123 (I-123) MIBG uptake in cardiac transplant recipients up to

5 months after transplantation, suggesting a lack of early cardiac reinnervation. However, cardiac autonomic reinnervation is likely to be a slow process. We now report our findings of I-123 MIBG imaging in cardiac transplant recipients 1 to 3 years after transplantation in an effort to document the presence or absence of cardiac reinnervation.

Methods

Patients. Twenty-three consecutive patients with New York Heart Association functional classes III and IV congestive heart failure underwent orthotopic cardiac transplantation at the University of California San Francisco between 1989 and 1992. All 23 patients agreed to participate in this research study. Ten of these patients have previously been reported on (16). The indications for orthotopic cardiac transplantation were idiopathic dilated cardiomyopathy (n = 12), ischemic cardiomyopathy (n = 10), and congestive heart failure due to rheumatic heart disease (n = 1). The study protocol and consent form were approved by the University of California San Francisco Committee on Human Research. All patients provided written informed consent.

All patients received graft rejection prophylaxis with cyclosporine, prednisone and azathioprine. Cyclosporine-associated hypertension was generally treated with diuretic drugs and a calcium channel blocking agent. Routine surveillance endomyocardial biopsies were performed after cardiac transplantation to rule out occult graft rejection. All patients underwent radionuclide ventriculography after transplantation to assess cardiac function. Patients also had annual exercise thallium scintigraphy and coronary angiography to rule out occult graft vasculopathy. Respiratory gas analysis was also performed at rest and at peak exercise.

Iodine-123 MIBG imaging. Unlabeled MIBG was obtained from the University of Michigan and was radioiodinated by solid-phase ammonium sulfate exchange (15). Four to eight millicuries of I-123 MIBG was injected as an intravenous bolus with patients in a relaxed, supine position. None of the patients were taking medications known to inhibit MIBG uptake. Serial dynamic imaging was performed at 30-s intervals, commencing just before the I-123 MIBG injection and continuing for 15 min. The scintillation camera (Siemens Orbitor, equipped with a low energy all-purpose collimator) was positioned in the anterior projection. Late images were not obtained because our previous work (16) has demonstrated that the human heart has little if any significant extraneuronal uptake, and hence early I-123 MIBG uptake is sufficient to demonstrate neuronal uptake. The presence or absence of I-123 MIBG uptake was assessed qualitatively. The intraobserver and interobserver agreement for detection of myocardial I-123 MIBG uptake was 100%. Myocardial I-123 MIBG uptake was quantified by measuring the heart/mediastinal ratio. In subjects with normal hearts at our institution, this ratio is 1.8 ± 0.1 (16). No correction for lung background was made for the qualitative assessment of cardiac uptake because 19 of the subjects served

as their own control, and there was no difference in lung background between the studies performed.

Nineteen patients underwent I-123 MIBG imaging at 3.8 ± 0.8 and 15.4 ± 4.7 months after cardiac transplantation. Two of these 19 patients also underwent imaging at 25 months. Two additional patients underwent I-123 MIBG imaging at 13.5 ± 0.7 and 25.5 ± 0.7 months after cardiac transplantation. One of these two patients also underwent imaging at 36 months. The final two patients underwent imaging only at 20 months after cardiac transplantation. No patients underwent imaging during active graft rejection of grade 1B or higher. All patients were clinically well and without symptoms of angina pectoris at the time of their MIBG imaging.

Transmyocardial norepinephrine release. Transmyocardial norepinephrine release was measured in 16 patients 21 ± 9.6 months after cardiac transplantation. Rest and supine single blood samples were obtained from the ascending aorta and coronary sinus at the time of routine surveillance angiography and were analyzed for norepinephrine concentrations. These blood samples were immediately centrifuged at 2,000 rpm for 15 min at 2 to 4°C. Plasma was separated and frozen at −70°C for later determination of norepinephrine concentrations using high pressure liquid chromatography with electrochemical detection (Smith Kline Beecham Laboratories). Transmyocardial norepinephrine release was calculated as coronary sinus norepinephrine minus aortic norepinephrine. The coefficient of variation for norepinephrine levels was 6.5%.

Statistics. Potential characteristic differences before and after cardiac transplantation between patients with positive and negative MIBG uptake results were analyzed by the unpaired Student t test. Potential differences in gender and disease status between patients with positive and negative MIBG uptake results were analyzed by the one-sided chi-square contingency table method; $p < 0.05$ was considered significant.

Results

Patients. Nineteen men and four women were studied (mean [±SD] age 50 ± 8.5 years) (Table 1). The mean left ventricular ejection fraction was 0.60 ± 0.07 determined 21 ± 7 months after cardiac transplantation. Three of 23 patients had minor reversible apical myocardial perfusion defects on exercise thallium scintigraphy; the remaining 20 patients had normal thallium scan results. No patient had evidence of graft coronary occlusive disease on annual coronary angiography.

Iodine-123 MIBG Imaging. None of 19 evaluable patients had visible cardiac uptake <5 months after cardiac transplantation (Fig. 1). Eleven (48%) of 23 patients demonstrated prominent anterior and basal myocardial I-123 MIBG uptake at 1 to 2 years after cardiac transplantation (Fig. 1). The I-123 MIBG heart/mediastinal ratio for the 11 images showing uptake was 1.7 ± 0.3; in 10 images without uptake this ratio was 1.2 ± 0.1 (p < 0.001). The majority of patients with cardiac I-123 MIBG uptake had a pretransplantation diagnosis of

Table 1. Clinical Characteristics of 23 Study Patients Before and After Cardiac Transplantation

	No MIBG Uptake (n = 12)	MIBG Uptake (n = 11)	p Value
Before cardiac transplantation			
Age (yr)	49.6 ± 9.4	51.2 ± 7.8	NS
Gender (M/F)	9/3	10/1	NS
Disease status			
Idiopathic	9	3	0.04
Ischemic/rheumatic	3	8	
After cardiac transplantation			
Follow-up (mo)	22.4 ± 8.8	19.5 ± 4.3	NS
Donor heart			
Age of donor (yr)	31.7 ± 10.8	36.0 ± 12.9	NS
Ischemic time (min)	153.7 ± 35.8	174.5 ± 44.6	NS
Average cyclosporine level (ng/ml)*	153.9 ± 70.2	122.1 ± 46.0	NS
Rejection grade 1A	2	2	
Rejection ≥ grade 1B	0	0	
Rest heart rate (beats/min)	89.1 ± 9.8	90.5 ± 12.1	NS
Peak exercise heart rate (beats/min)	135.3 ± 21.4	130.0 ± 19.2	NS
Peak exercise systolic blood pressure (mm Hg)	149.1 ± 16.5	160.1 ± 22.6	NS
Peak exercise oxygen consumption (ml/kg per min)	19.6 ± 5.0	15.9 ± 2.9	NS
Left ventricular ejection fraction	0.61 ± 0.08	0.58 ± 0.05	NS

*Average cyclosporine trough whole-blood levels as determined at routine phlebotomies for follow-up visits (measured by high performance liquid chromatography). Data presented are mean value ± SD or number of patients. F = female; M = male; MIBG = metaiodobenzylguanidine.

ischemic cardiomyopathy or rheumatic heart disease (8 [73%] of 11). In the 12 patients without cardiac I-123 MIBG uptake, 3 (25%) had a pretransplantation diagnosis of ischemic car-

Figure 1. Iodine-123 (I-123) metaiodobenzylguanidine (MIBG) scintigraphic images taken at 5, 10 and 15 min after injection at 3 months and 1 year after transplantation in an individual heart transplant recipient. After blood pool clearance there is an absence of I-123 MIBG myocardial localization at 3 months, which is present at 1 year after transplantation. S/P = status post.
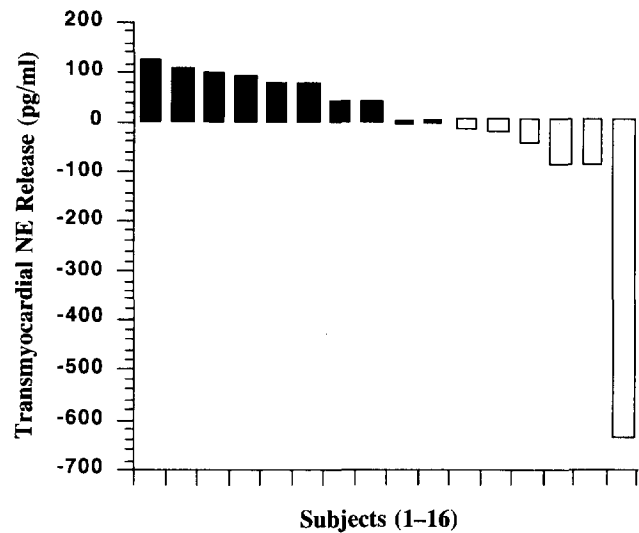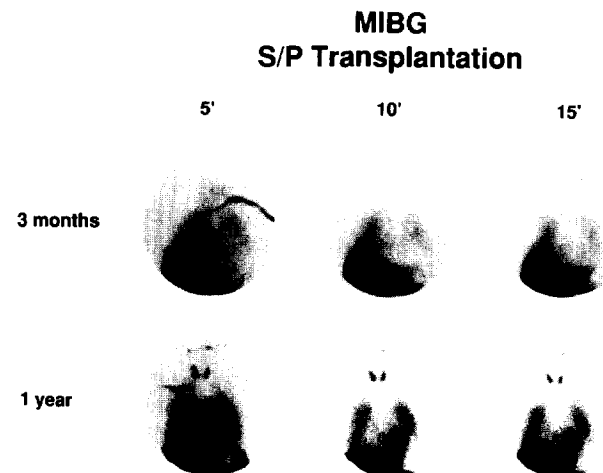

Figure 2. Correlation between cardiac iodine-123 (I-123) metaiodobenzylguanidine (MIBG) uptake and transmyocardial release of norepinephrine (NE). Positive norepinephrine values indicate net transmyocardial norepinephrine release. **Solid bars** = cardiac I-123 MIBG uptake; **open bars** = no cardiac I-123 MIBG uptake.

diomyopathy (Table 1), and 9 had idiopathic dilated cardiomyopathy (p = 0.04). There were no other significant differences in characteristics before and after cardiac transplantation between patients with and without I-123 MIBG uptake. (Table 1). When only the 19 patients with serial images were analyzed, 10 (53%) had evidence of late I-123 MIBG cardiac uptake, 8 of whom had a pretransplantation diagnosis of ischemic cardiomyopathy or rheumatic heart disease. In contrast, seven (78%) of nine patients without I-123 MIBG cardiac uptake had a pretransplantation diagnosis of idiopathic dilated cardiomyopathy (p = 0.04). Two patients in each group (I-123 MIBG uptake present or absent) underwent late imaging when endomyocardial biopsy results showed grade 1A rejection (Table 1).

Transmyocardial norepinephrine release. Transmyocardial release of norepinephrine was determined in 16 subjects a mean of 23 ± 7.6 months (range 15 to 30) after cardiac transplantation (Fig. 2). All 10 patients with cardiac I-123 MIBG uptake demonstrated a net release across the heart. In contrast, all six patients without cardiac I-123 MIBG uptake failed to demonstrate a net release of norepinephrine across the heart.

Discussion

Iodine-123 MIBG Imaging. The presence of cardiac I-123 MIBG uptake in nearly 50% of our subjects indicates that autonomic reinnervation occurs frequently in the human transplanted heart. Serial I-123 MIBG scans in our subjects demonstrate that significant reinnervation is delayed because I-123 MIBG cardiac uptake is only demonstrable ≥1 years after transplantation. In human transplanted hearts, cardiac sympathetic neurons are severed from their cell bodies in thoracic

and cervical ganglia. Norepinephrine stores in the cardiac nerve terminals are rapidly depleted because the biochemical machinery needed to synthesize norepinephrine must be transported from the native ganglion to the nerve terminal by axonal transport (17,18). Intact adrenergic innervation of the heart is the principal determinant of myocardial norepinephrine production (19,20). Metaiodobenzylguanidine has uptake and storage properties similar to norepinephrine but is not metabolized by monoamine oxidase or catechol o-methyl transferase (12). Metaiodobenzylguanidine localizes to the adrenal medulla, adrenergic nerves and myocardium in several animal species, including humans (15,21,22). The presence of I-123 MIBG cardiac uptake late after cardiac transplantation provides evidence of autonomic reinnervation in the transplanted heart.

Within 1 year of cardiac transplantation, the lack of cardiac autonomic reinnervation can be demonstrated by the reproducible attenuation of the heart rate response to exercise (23–26); low myocardial norepinephrine content (17,26–31); rarity of nerves seen in anatomic specimens of transplanted hearts (32,33); and lack of cardiac I-123 MIBG uptake (16,34). Several lines of evidence support the finding that reinnervation occurs in the human transplanted heart >1 year after graft placement. First, cohort studies (25,26,30,31) have examined the physiologic response of cardiac transplant recipients to adrenergic stimuli "early" (2 to 14 months) and "late" (12 to 102 months) after transplantation. These studies all demonstrate an improvement in the attenuation of the normal heart rate response to exercise (25,26), orthostasis (25), hand-grip exercise (26,30) or tyramine release (a chemical that stimulates norepinephrine release from intact sympathetic nerve terminals) (31) in patients late versus early after transplantation. Second, anginal chest pain has been reported in two patients 36 months after cardiac transplantation (10). Both patients had angiographically confirmed graft coronary vasculopathy. Third, cohort studies have demonstrated a significant increase in cardiac norepinephrine release or spillover after exercise (26), hand-grip exercise (30) and tyramine administration (10,31) in patients late versus early after transplantation. Our data provide strong confirmation of the ability of the transplanted human heart to reinnervate, both in terms of the development over time of I-123 MIBG uptake on cardiac images and in terms of the 100% correlation between the presence (or absence) of I-123 MIBG uptake on cardiac images and the presence (or absence) of transmyocardial norepinephrine release.

In our protocol, we studied patients serially over time with multiple I-123 MIBG scans. Patients therefore acted as their own controls, and we were able to document that 11 patients with early negative findings on I-123 MIBG scans later had positive findings. Our study design differs from that of previously mentioned studies, which did not perform serial examinations of their subjects.

Our use of I-123 MIBG scintigraphy also confirms previous work (11) with positron emission tomography to examine the question of cardiac graft reinnervation. Schwaiger et al. (11)

reported cardiac uptake of carbon-11 hydroxyephedrine 5.3 ± 3.0 months after cardiac transplantation. Carbon-11 hydroxyephedrine is a catecholamine analogue and its uptake in the heart, like MIBG, indicates the presence of intact sympathetic nerve terminals. The positron emission tomographic scan images showed uptake in the proximal anterior and septal walls of the heart, a finding consistent with our I-123 MIBG scan images predominantly of the proximal anterior and basal myocardium. Thus, the pattern of reinnervation recapitulates the normal pattern of early sympathetic neuronal ingrowth and distribution in the heart (high neuronal density at the base and progressively less density toward the apex) (36).

Although this study and previous studies have demonstrated that late reinnervation can occur in a significant proportion of cardiac transplant recipients, the clinical significance of this phenomenon remains unknown. In our subjects, there was no difference in heart rate, systolic blood pressure or oxygen consumption at peak exercise between those patients who developed myocardial I-123 MIBG uptake and those who did not (Table 1). Therefore, initial evidence of sympathetic reinnervation did not have physiologic functional consequences in our subjects. It is possible that physiologic consequences of reinnervation may be delayed from the first evidence of I-123 MIBG uptake and that serial exercise tests with peak oxygen consumption determination may eventually become significant.

Numerous questions remain regarding the phenomenon of cardiac reinnervation. Among these is, "Do all transplanted hearts become reinnervated over time?" A surprising finding in our study was that 73% of patients who underwent transplantation for ischemic cardiomyopathy (n = 7) or rheumatic heart disease (n = 1) eventually had reinnervation of their heart compared with only 25% of those undergoing transplantation for idiopathic dilated cardiomyopathy (p = 0.04). The patient numbers are small, but this suggests that the underlying pathophysiology of heart failure might influence the kinetics and eventuality of reinnervation after cardiac transplantation. Autoantibodies against the $beta_1$-adrenoceptor and against the adenosine diphosphate/adenosine triphosphate carrier in the inner mitochondrial membrane have been described in patients with idiopathic dilated cardiomyopathy (36,37). Could patients with idiopathic cardiomyopathy be producing antiautonomic neuronal antibodies? Patients with diabetes mellitus have been shown to produce antiautonomic neuronal antibodies (38). These patients develop an autonomic neuropathy and demonstrate decreased cardiac I-123 MIBG uptake (13,39). Patients with idiopathic dilated cardiomyopathy have decreased cardiac I-123 MIBG retention (34). There may be a common link between the pathophysiology of cardiomyopathy and the relative lack of reinnervation after cardiac transplantation in this group of patients. A larger number of patients will be needed to determine with certainty whether there is a true difference in the reinnervation rates of patients with idiopathic versus ischemic cardiomyopathy after cardiac transplantation.

Transmyocardial norepinephrine release. In the present study, excellent correlation was found between myocardial

norepinephrine release and I-123 MIBG uptake. Norepinephrine release may indicate decreased reuptake or increased synthesis and release, or both. Whatever the mechanisms for higher norepinephrine concentration in the coronary sinus in patients with I-123 MIBG uptake, norepinephrine release probably represents active myocardial norepinephrine metabolism, providing further evidence for sympathetic reinnervation.

Conclusions. Our findings confirm the late reinnervation of the human heart after transplantation. Reinnervation occurs predominantly in the anterior and basal myocardium where adrenergic nerve density is greatest in the normal human heart. The functional consequences of a partially reinnervated heart are unknown. It appears that more transplant recipients with ischemic cardiomyopathy will have reinnervation of their heart than those with idiopathic dilated cardiomyopathy.

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